## REMARKS

Claims 1, 3-5, 7-14, 17, 31-55 and 57-90, and 94-96 are pending in the present application. By virtue of this response, claims 1, 9, and 17 have been amended by incorporating the limitations of claims 58, 61, and 71, respectively. Claims 58, 61, 71, and 85-90 are cancelled. Upon entry of the present amendment, claims 1, 3-5, 7-14, 17, 31-55, 57, 59-60, 62-70, and 72-84, and 94-96 are under consideration. No new matter is added.

With respect to claim amendments and cancellation, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

### *Claim Rejections – 35 USC § 103*

***Rejection based on Desai in view of Kunz further in view of Westesen***

Claims 1, 3-5, 7-14, 17, 31-33, 38-41, 46-49, 54-55, and 57-96 are rejected under 35 U.S.C. § 103(a) on the ground that these claims are allegedly unpatentable over Desai et al. ("Desai," 5,439,686), in view of Kunz et al. ("Kunz," 5,733,925) in further view of Westesen et al. ("Westesen," 6,197,349). Applicants respectfully traverse this rejection.

Solely in an effort to expedite prosecution, claims 1, 9, and 17 have been amended to incorporate the limitations of claims 58, 61, and 71 respectively to recite "wherein the average diameter of the nanoparticles in the composition is no greater than about 200 nm." Applicants maintain arguments previously presented and respectfully submit that the cited references, alone or in combination, do not teach or suggest the invention claimed in the present application.

In response to Applicants' previous arguments, the Examiner states that "Kunz does not teach instant coated composition and instead has been cited for the claimed method," and that the modification of the teachings of Desai with the teachings of Kunz and Westesen results in the claimed methods. Page 9, second full paragraph of the Office Action. Applicants respectfully submit that one of ordinary skill in the art would not have been motivated to use the particle compositions of Desai for carrying out the methods of Kunz for the purpose of treating a vascular hyperplasia such as restenosis.

According to Kunz, an effective treatment of a vascular hyperplasia, namely, restenosis, would entail: a) delivering a large number of molecules into the intracellular spaces between smooth muscle cells, b) directing an inhibitory drug into the proper intracellular compartment, and c) optimizing the association of the inhibitory drug with its intracellular target while minimizing intracellular redistribution of the drug, e.g., to neighboring cells. Column 2, lines 37-46 of Kunz. Kunz also teaches that, because smooth muscle cell proliferation takes place over several weeks, it would appear *a priori* that the inhibitory drug be administered over several weeks, perhaps continuously, to produce beneficial effects. Column 2, lines 47-50 of Kunz. The methodologies disclosed in Kunz were developed to specifically address these issues and considerations for treating hyperplasia of non-cancerous cells in a blood vessel.

As discussed below in more detail, one of ordinary skill in the art reading Desai would not have used the particle compositions of Desai for carrying out the methods of Kunz and would not have expected that the composition of Desai, when administered by following the administration regime recited in the present claims, would allow effective treatment of hyperplasia of non-cancerous cells in the blood vessel.

Specifically, Desai discloses "particles having radii fall in the range of about 0.1 up to about 5 micron," namely, particles having a size range of 200 nm to 10,000 nm. Desai further teaches that, after intravenous/intraarterial injection, "particles less than about 2 microns will be rapidly cleared from the blood stream by the reticuloendothelial system (RES), also known as the mononuclear phagocyte system (MPS)." Desai, col. 2, lines 30-37. According to Desai, "[d]ue to

the microparticular nature of the delivered drug [in Desai's formulations], most of it is cleared from the circulation by organs having reticuloendothelial systems such as the spleen, liver, and lungs. This allows pharmacologically active agents in particulate form to be targeted to such sites within the body." Desai, col. 10, lines 43-48. Given the teaching in Desai that most of its particles administered would be cleared from the circulation by organs having RES, one of ordinary skill in the art would not have been motivated to use the particle compositions of Desai for carrying out the methods of Kunz for the purpose of treating a vascular hyperplasia such as restenosis.

Furthermore, given the teaching in Kunz that an effective treatment of a vascular hyperplasia, namely, restenosis, would entail delivering a large number of molecules into the intracellular spaces between smooth muscle cells, one would not reasonably expect that administering the particle composition of Desai would result in high enough local concentration of the drug that allows effective treatment of hyperplasia of non-cancerous cells in a blood vessel, especially when the composition is administered by following the administration regime recited in the present claims.

Westesen does not cure the deficiencies of Desai and Kunz discussed above. Specifically, Westesen is cited as allegedly teaching an amorphous form of a drug for better solubility and availability. Westesen is completely silent about treatment of hyperplasia of non-cancerous cells in a blood vessel, much less treatment of hyperplasia of non-cancerous cells in a blood vessel by administering a nanoparticle composition recited in the present claims and following the specific administration regime recited in the present claims.

The presently claimed invention is based on the surprising finding that a nanoparticle composition comprising a drug in amorphous form having an average diameter of no greater than about 200 nm, coated with a coating consisting essentially of protein, "when administered systemically, can markedly reduce the level of restenosis following balloon angioplasty and stenting," and "can markedly reduce the level of intimal hyperplasia or neointima formation following systemic administration." Page 8, lines 1-7 of the present application. Such nanoparticles

(hereinafter referred to as "albumin coated drug nanoparticles") were surprisingly found to accumulate in high concentration in tissues not containing the RES, including the heart. *See* WO99/00113, page 27, line 16 to page 28, line 8 (previously submitted as Exhibit A accompanying the response to Office Action filed on October 12, 2006). As shown in the present application, transient exposure of the albumin-coated drug nanoparticles, for example by systemic administration in 30 minutes or less, was able to provide a drug concentration at the site of injury that was sufficient to suppress neointimal hyperplasia. Page 25, lines 18-21 of the present application. Examples 7-18 of the present application demonstrate the remarkable effect of the albumin-coated paclitaxel nanoparticle composition on treatment of restenosis when infused over a period of only five minutes.

Thus, given the teaching in Kunz that an effective treatment of vascular hyperplasia would entail delivering a large number of molecules into the intracellular spaces between smooth muscle cells, and the teaching in Desai that most of Desai's particles would be cleared from the circulation by organs having RES, one of ordinary skill in the art would not have been led to use the particle compositions of Desai for carrying out the methods of Kunz with a reasonable expectation of success, especially when the composition is administered by following the administration regime recited in the present claims. The remarkable results by carrying out methods of the present claims cannot be expected based on the teachings of the cited references.

Accordingly, Applicants respectfully submit that Desai, Kunz, and Westesen, alone or in combination, do not render the claimed invention obvious. Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

***Rejection based on Desai in view of Hunter in further view of Westesen***

Claims 1, 3-5, 7-14, 17, 31-36, 38-43, 46-51, 54-55, and 57-96 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Desai ("Desai," 5,439,686) in view of Hunter et al. (5,716,981, "Hunter") in further view of Westesen. Applicants respectfully traverse this rejection.

In response to Applicants' previous arguments, the Examiner states that "Hunter is taught for the use of paclitaxel for treating hyperplasia and the teaching of a nanoparticle of protein shell comprising the drug comes from Desai." Page 18, first paragraph of the Office Action.

As discussed above, Desai teaches particles having a size range of 200 nm to 10,000 nm. Desai further teaches that, after intravenous/intraarterial injection, most of the particles are cleared from the circulation by organs having RES such as the spleen, liver, and lungs. Given the teaching in Desai that most of the particles administered would be cleared from the circulation by organs having RES, one of ordinary skill in the art would not have been motivated to use the particle compositions of Desai for the purpose of treating restenosis.

Further, although Hunter provides a general statement that the antiangiogenic compositions disclosed therein may be prepared for administration by different routes, including for example intravenous administration, it provides no guidance for choosing the particular claimed administration regime for treating hyperplasia of non-cancerous cells in a blood vessel. Given the special issues and considerations discussed above for treating hyperplasia of non-cancerous cells in a blood vessel, one of ordinary skill in the art would not have reasonably expected that treatment of vascular hyperplasia would be effective by following the broad general teachings of Hunter on systemic administration.

Westesen does not cure the deficiencies of Desai and Hunter. As discussed above, Westesen is cited as allegedly teaching an amorphous form of the drug (poorly soluble drug) for better solubility and availability. Westesen is completely silent about treatment of hyperplasia of non-cancerous cells in a blood vessel, much less treatment of hyperplasia of non-cancerous cells in a blood vessel by administering a nanoparticle composition recited in the present claims and following the specific administration regime recited in the present claims.

Accordingly, Applicants respectfully submit that Desai, Hunter, and Westesen, alone or in combination, do not render the claimed invention obvious. Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

***Rejection based on Desai in view of Kunz or Hunter further in view of Westesen further in view of Gregory***

The Examiner further maintained her rejection for claims 36-37, 44-45 and 52-53 under U.S.C. § 103(a) on the ground that these claims are allegedly being unpatentable over Desai et al. ("Desai," 5,439,686) in view of Kunz et al. ("Kunz," 5,773,925) or Hunter ("Hunter," 5,716,981) respectively in view of Westesen et al. ("Westesen," 6,197,349) in further view of Gregory ("Gregory," Transplantation, vol. 59, pp. 655-661, 1995). Applicants respectfully traverse this rejection.

Desai, Kunz, Hunter, and Westesen are discussed above. Applicants respectfully submit that these references, alone or in combination, do not render the claims of the present invention obvious.

Gregory is cited as allegedly teaching that rapamycin is an immunosuppressant which has an antiproliferative action that is useful in the treatment of arterial thickening after injury such as angioplasty. Gregory does not cure the deficiencies discussed above.

Accordingly, Applicants respectfully submit that the cited references do not render claims of the present application obvious and respectfully request that the 35 U.S.C. § 103 rejection be withdrawn.

***Rejection based on Hunter by itself or in view of Yapel further in view of Kunz and Westesen***

Claims 1, 3-5, 7-14, 17, 31-33, 34-35, 38-41, 42-43, 46-49, 50-51, 54-55, and 57-96 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hunter et al. ("Hunter," 5,716,981) by itself or in view of Yapel ("Yapel," 4,147,767) in further view of Kunz et al.

("Kunz," 5,733,925) and Westesen et al. ("Westesen," 6,197,349). Applicants respectfully traverse this rejection.

Applicants maintain arguments previously presented and respectfully submit that the cited references, alone or in combination, do not teach or suggest the claimed invention.

In response to arguments previously presented by Applicants, the Examiner states that "Hunter is taught for the use of paclitaxel in treating hyperplasia and the teaching of a nanoparticle of protein shell comprising the drug comes from Desai." Page 24, last paragraph of the Office Action.

Applicants respectfully submit that the rejection in this section is not based on Desai, and that the Examiner has failed to establish which reference other than Desai provides the teaching of the nanoparticle compositions recited in the present claims.

Neither Hunter nor Kunz teaches or suggests administering an effective amount of a composition comprising an amorphous drug in nanoparticle form, coated with a coating consisting essentially of protein, wherein the effective amount of the composition is systemically administered in 30 minutes or less, and wherein the average diameter of the nanoparticles in the composition is no greater than about 200 nm.

Furthermore, as discussed above, Desai teaches particles having a size range of 200 nm to 10,000 nm. Desai further teaches that, after intravenous/intraarterial injection, most of the particles are cleared from the circulation by organs having RES such as the spleen, liver, and lungs. Given the teaching in Desai that most of the particles administered would be cleared from the circulation by organs having RES, one of ordinary skill in the art would not have been motivated to use the particle compositions of Desai for the purpose of treating restenosis.

Westesen does not cure the deficiencies of the references discussed above. Specifically, Westesen is cited as allegedly teaching an amorphous form of the drug (poorly soluble drug) for better solubility and availability. Westensen is completely silent about treatment of hyperplasia of non-cancerous cells in a blood vessel, much less treatment of hyperplasia of non-cancerous cells in a blood vessel by administering a nanoparticle composition recited in the present claims and following the specific administration regime recited in the present claims.

Yapel does not cure the deficiencies of Hunter, Kunz, and Westesen. Yapel is "only relied upon to provide further motivation to utilize albumin." Page 26, first paragraph of the Office Action. Yapel is completely silent about treatment of hyperplasia of non-cancerous cells in a blood vessel, much less treatment of hyperplasia of non-cancerous cells in a blood vessel by administering a nanoparticle composition recited in the present claims and following the specific administration regime recited in the present claims.

Accordingly, Applicants respectfully submit that the cited references do not render claims of the present application obvious and respectfully request that the 35 U.S.C. §103 rejection be withdrawn.

***Rejection based on Hunter by itself or in view of Yapel in view of Kunz and Westesen further in view of Marx***

Claims 36-37, 44-45, and 52-53 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hunter et al. ("Hunter," 5,716,981) by itself or in view of Yapel ("Yapel," 4,147,767) in view of Kunz et al. ("Kunz," 5,733,925) and Westesen et al. ("Westesen," 6,197,349) in further view of Marx ("Marx," Circ. Res. Vol. 76, pp. 412-417, 1995). Applicants respectfully traverse this rejection.

As discussed above, Hunter, Yapel, Kunz, and Westesen, alone or in combination, do not render claims of the present application obvious. Marx is cited as allegedly disclosing rapamycin as

an inhibitor of smooth muscle cells in the abnormal proliferation of restenosis. Marx does not cure the deficiencies discussed above.

Accordingly, Applicants respectfully submit that the cited references do not render claims of the present application obvious and request that the 35 U.S.C. § 103 rejection be withdrawn.

***Double Patenting***

Claims 1, 3-5, 7-14, 17, 31-33, 38-41, 46-49, 54-55, and 57-96 are provisionally rejected under obviousness-type double patenting over claims 1-2 and 5-18 of 11/594,417. Claims 1, 3-14, 17, 31-33, 38-41, 46-49, 54-55, and 57-96 are provisionally rejected under obviousness-type double patenting over claims 1-7, 11-20, and 44-45 of 11/359,286 in view of Hunter and Westesen.

Applicants submit that patent application No. 11/594,417 is abandoned, thus rendering the rejection moot. In addition, claims 58, 61, 71, and 85-90 have been canceled, thus rendering rejection of these claims moot. Applicants further respectfully request that these provisional rejections based on patent application No. 11/359,286 be held in abeyance until the Office has made a determination of otherwise allowable claims in the present application or in patent application Nos. 11/359,286.

## CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 638772000127. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

Electronic signature: /Jian Xiao/
Jian Xiao
Registration No.: 55,748
MORRISON & FOERSTER LLP
755 Page Mill Road
Palo Alto, California 94304-1018
(650) 813-5736